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EDITORIAL COMMENT

Diabetes and Heart Failure

The Role of Thiazolidinediones in Managing These Partners in Crime*

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Over 30 years ago, data from the Framingham cohort established a link between diabetes mellitus (DM) and heart failure (HF) (1). Most HF trials have since shown a 25% to 35% prevalence of DM in HF populations. Diabetes mellitus is associated with an increased mortality and hospital readmission rate in patients with HF, and uncontrolled DM and hyperglycemia reduce the effectiveness of standard HF therapies (2,3). The increasing age and the obesity epidemic in our society are increasing the incidence and prevalence of both DM and HF.

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Diabetes mellitus is a major risk factor for the development of HF through its propagation of atherosclerotic cardiovascular disease, diabetic cardiomyopathy, and nephropathy. Diabetes mellitus and hyperglycemia evoke lipid disorders, endothelial dysfunction, platelet hyperreactivity, an elevation of proinflammatory cytokines, circulating free fatty acids and adhesion molecules, and oxidative stress of myocardium. These derangements must adversely affect the pathophysiology and clinical course of HF. However, their impact does not simply begin with established DM. Prediabetes–insulin resistance itself is associated with left ventricular (LV) dysfunction, HF, and increased cardiovascular mortality (4–6). Each 1% elevation of glycosylated hemoglobin (HbA1c) can be linked to an 8% increased risk of HF, and hyperglycemia over time increases HF symptoms. Heart failure itself engenders insulin resistance, and in turn, the insulin resistance adversely affects HF and fosters HF as an atherogenic condition (7–10).

Thiazolidinediones (TZDs) reverse or ameliorate many of the adverse cardiovascular effects of DM (11–13). The TZDs increase insulin sensitivity, enhance glucose control, improve the lipid profile, suppress inflammatory and cardiovascular risk markers, reduce proinflammatory cytokines, augment endothelial function, and improve vascular structure and function. The TZDs now have been shown to substantially reduce the development of DM in patients with prediabetes (14). They decrease mortality, stroke, and myocardial infarction rates in patients with type II DM (15).

These favorable properties should make TZDs ideal for the management of patients with both DM and HF. However, case reports and a number of retrospective studies have raised concern that TZDs exacerbate clinical HF (16–20).

The TZDs, like many antihyperglycemic agents, increase body weight during long-term administration. The added weight produced by TZDs is secondary to an increase in peripheral obesity (but less visceral fat) and fluid volume. In general DM populations, monotherapy with TZDs is associated with a net 3% to 5% incidence of pedal edema and a net <1% incidence of clinical HF (18). When combined with other oral antihyperglycemic agents, the incidence of pedal edema increases to 6% to 8% (1% to 3% in non–TZD-treated patients), and with a further increase to 13% to 17% in patients concomitantly treated with insulin (4% to 7% in non-TZD insulin-treated patients) (18). The mechanism of TZD-induced edema has not been convincingly established.

Pedal edema is often a multifactorial process, not necessarily attributable to HF alone. From an insurance database, Delea et al. (16) reported an adjusted incidence of developing clinical HF of 8.2% in patients when TZDs were added to other DM therapy versus 5.3% in those continued on similar therapy without TZDs, a net incidence of 2.9% over the 40-month study period. Although adjusted for analyses, the patients in the TZDs group had a higher prevalence of underlying (pre-TZDs) problematic coronary artery disease, diabetic complications, insulin therapy, and other comorbidities. Judging from the higher background use of angiotensin-converting enzyme inhibitors and beta-blocking agents in the TZDs group, it is likely that unrecognized or unrecorded HF or systemic hypertension also were more prevalent in the TZD treatment group. Using a Kaiser Permanente database, Karter et al. (21) reported that initiating monotherapy for DM with TZDs did not increase hospitalization rate for HF over a mean follow-up period of 10.2 months compared with initiating sulphonylureas or insulin.

The biggest challenge for the safe use of TZDs in DM resides in the patients with concomitant HF. A retrospective study by Tang et al. (17) showed that 17.1% (19 of 111) of their patients with both DM and systolic HF (LVEF <45%, New York Heart Association functional class [NYHA FC] I to III) experienced weight gain plus pedal edema, 5.4% (6 of 111) developed jugular venous distention, and 1.8% (2 of 111) showed clinical or radiographic signs of pulmonary edema while on TZD therapy. Echocardio-

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graphic testing in this study did not uncover adverse effects of TZDs on cardiac function. Data from larger studies appear more benign. From a Medicare database, Inzucchi et al. (21) found that TZDs over 1 year resulted in only a borderline increase in the risk of hospitalization for HF (hazard ratio [HR] 1.09, 95% confidence interval [CI] 1.00 to 1.20) in elderly diabetic patients after myocardial infarction. The TZDs did not impact mortality in this study. A similarly low rehospitalization risk for HF (HR 1.06, 95% CI 1.00 to 1.09) was found by Masoudi et al. (22) in elderly patients with both DM and HF; interestingly, TZDs were associated with a lower risk of death (HR 0.87, 95% CI 0.80 to 0.94) at 1 year. And now, in over 4,500 outpatients with both DM and HF in the Veterans Administration database reported by Aguilar et al. (23) in this issue of the *Journal*, ambulatory DM-HF patients did not experience an increase in hospitalization rate (covariate adjusted HR 1.00, 95% CI 0.81 to 1.24) or mortality (HR 0.98, 95% CI 0.81 to 1.17) when treated with TZDs compared with those not receiving TZDs.

The authors of this editorial were pleased to see the results of the Aguilar et al. (23) study, along with those of Karter et al. (21) and Masoudi et al. (22), because we have prescribed TZDs in diabetic HF patients with the view that HF therapy is more effective when DM is better controlled, and that the cumulative beneficial effects of TZDs over time exceed their major shortcoming (other than cost), namely detectable fluid retention in <10% of HF patients. Furthermore, problematic fluid retention by TZDs is readily reversed by discontinuing the TZDs or reasonably controlled by those experienced with HF management. Simple pedal edema without problematic intravascular fluid retention is even less of a threat; never in the history of mankind have we ever lost someone to pedal edema alone.

There is still a dearth of data relative to the use of TZDs in diabetic HF patients. Interpretable data are mostly available for NYHA FC I to II patients. All studies to date are retrospective, gleaned from database information. Most reports placed emphasis on safety rather than potential cardiovascular benefits; in contrast to monitoring the adverse effects of TZDs, the identification of beneficial clinical effects and outcomes are likely to require studies of considerably longer duration and greater complexity. Studies in NYHA FC III patients are limited at best. Studies in NYHA FC IV patients could be of interest, but have a low sales potential to inspire industrial support. In addition, it is hard to imagine how TZDs could favorably impact the extreme mechanisms and dire clinical status of this patient subgroup during their typical short-term existence.

Because HF itself evokes insulin resistance, it is not unreasonable to suggest that TZDs be studied prospectively in non-DM NYHA FC I to III HF patients. Furthermore, should TZDs be considered for primary prevention of heart disease and HF in prediabetic subjects who have not yet met the criteria for the diagnosis of DM and the standard eligibility for antihyperglycemic therapy? In such a patient population, the results of the DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) trial (14) showed that rosiglitazone at 8 mg daily over a median follow-up of 3 years reduced the relative occurrence of DM by 60% and achieved normoglycemia in 70% to 80% at a net risk of developing clinical HF in only 0.4% (TZDs 0.5%, placebo 0.1%). Parenthetically, hypoglycemia is an uncommon adverse effect of TZDs when not combined with other antihyperglycemic therapy. Until the results of prospective trials are available, the report of Aguilar et al. (23) and others noted above should at least keep TZDs out of the dreaded "black box" warning for HF, and even raise the question of whether we should expand the clinical application of TZDs in LV dysfunction and HF rather than limit or restrict such. Using a manageable adverse property occurring in <10% of recipients to deny the beneficial effects of TZDs in the remaining 90% (and perhaps in many of the 10% group as well) is not shrouded in wisdom.

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